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A BITTERSWEET BALANCE: ADJUNCT THERAPY FOR HYPERGLYCEMIA IN
CRITICALLY ILL PATIENTS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree
Master of Medical Science

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Abstract

Stress-induced hyperglycemia in critically ill patients negatively affects their recovery. Providers have struggled to balance the treatment of hyperglycemia with aggressive insulin therapy with the risk of hypoglycemia as an adverse effect. Both immobilization and continuous enteral nutrition are common in a critical care setting and have implications as contributors for further hyperglycemia due to decreased peripheral glucose uptake and worsening insulin resistance. We propose to determine if an aggressive early mobilization protocol and nutrition protocol in the form of bolus feeds will decrease the amount of insulin units needed to treat hyperglycemia in critically ill patients. To do so, patients over 18 years old will be randomized to one of four intervention groups receiving either standard of care and/or intervention nutrition and mobilization protocol, in a medical intensive care unit at two campuses of an academic institution. The results could change the management of hyperglycemia in critically ill patients, limiting the amount of insulin units required and lowering the risks of hypoglycemia.

Chapter 1 – Introduction

Background

Stress Hyperglycemia

In critical illness, patients often become hyperglycemic (defined as a fasting blood glucose $\geq 126\text{mg/dL}$ or a random blood glucose $>200\text{mg/dL}$ ¹). Hyperglycemia is an evolutionary adaptive response to stress by the hypothalamic-pituitary-adrenal axis, sympathoadrenal system and proinflammatory cytokines to synergistically increase available glucose². A complex combination of endogenous and exogenous factors contribute to hyperglycemia such as increased insulin resistance, decreased insulin production, increased glucose levels (secondary to failure to suppress gluconeogenesis as well as administration of nutritional support with excess glucose), and/or increased counter-regulatory hormones controlling the whole process³.

While partially adaptive, this stress hyperglycemia has downstream consequences for the body and impacts recovery from critical illness. Hyperglycemia can lead to fluid depletion, hypoperfusion, and electrolyte loss and additionally has negative cellular

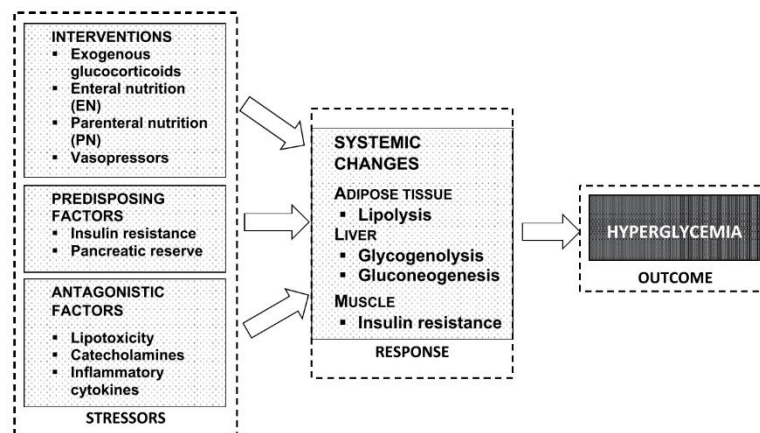


Figure 1. Mechanisms of Stress-Induced Hyperglycemia⁴

effects including mitochondrial injury, neutrophil dysfunction, and endothelial dysfunction⁵. On a molecular level, it can lead to oxidant injury, protein glycation, and complement inhibition. Taken together, in a wide variety of disease states, uncontrolled hyperglycemia has been associated with increased mortality as well as morbidity from complications such as infections⁶.

Intensive Insulin Therapy

Given the known physiologic consequences of over-exuberant excursions in blood glucose levels, researchers and providers have attempted to address this problem of hyperglycemia and minimize its effects on patient recovery and mortality. Early studies looked at aggressive and early implementation of intensive insulin therapy (IIT) to maintain a target blood glucose of 80-110mg/dL. A landmark study performed in a surgical intensive care unit (SICU) in Leuven, Belgium comparing insulin treatment of hyperglycemia with IIT versus a more conservative target blood glucose of <180mg/dL showed a statistically significant and successful reduction in morbidity and mortality in the IIT group⁷. Another study by the same research team looked at the effects of IIT in the medical intensive care unit (MICU) and again showed an overall reduction in morbidity, but a reduction in mortality was only seen among patients staying in the intensive care unit (ICU) for more than 3 days⁸. These studies helped solidify IIT's place in standard clinical practice in the ICU which was quickly endorsed by multiple professional societies.

However, in subsequent years, further studies have had conflicting results and led to equipoise, leaving providers less certain about the benefits of aggressive hyperglycemia management among critically ill patients⁹⁻¹². For example, two studies by

Prieser et al. and Brunkhorst et al. demonstrated an increased risk for serious adverse effects related to hypoglycemia and no significant difference in mortality among patients receiving IIT compared to a more modest blood glucose target of 140-180 mg/dL^{10,11}. In the large randomized trial, Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR), researchers found that IIT with a blood glucose target of 81-108mg/dL compared to a moderate glucose target of 140-180mg/dL actually increased mortality among critically ill patients and led to significantly more hypoglycemic episodes (defined as <40mg/dL)¹³.

While some have questioned the magnitude of harm related to hypoglycemic events occurring in a closely monitored ICU setting where appropriate treatment is promptly administered, the concern regarding severe hypoglycemia rates seems warranted. Severe hypoglycemia is independently associated with increased mortality in several studies¹⁴. In the ICU, both severe hypoglycemia and multiple hypoglycemic events within the same patient have been associated with increased 90 day mortality¹⁵. Given that attempts to control blood glucose values with insulin always come with some price in terms of increasing hypoglycemia rates no matter how carefully a glucose management protocol is followed, the ideal target blood glucose range (balancing the hyper- and hypoglycemia associated risks) as well as novel (non-insulin dependent) interventions that ameliorate the insulin resistant state during critical illness have been under discussion. Leveraging early mobilization as well as optimizing nutrition delivery may be examples of non-insulin dependent means to improve glucose control in the ICU, but there are few studies which have specifically examined this.

Mobilization in the ICU – Benefits and Its Impact on Glycemic Control

In recent years, immobilization and lack of aggressive physical therapy (PT) have also been associated with morbidity in the ICU. As a corollary, implementation of an ICU mobilization protocol has been associated with improved patient outcomes. While improvement in patient outcomes have been attributed to a number of factors, such as fewer delirium days and sedation holidays¹⁶, one of the added benefits of ICU mobilization may be improved glycemic control. Significant insulin resistance has been associated with limitations on physical activity, such as seen in a bedbound ICU patient¹⁷. Immobility and ICU-acquired weakness have been shown to increase insulin resistance and reduce peripheral glucose uptake¹⁸.

During physical activity, the contracting muscle increases rate of glucose uptake, and these benefits can last for hours after exercise¹⁹. A secondary analysis of a previous study showed that early mobilization in ICU patients was associated with decreased need for insulin to maintain euglycemia (0.07units/kg/day versus 0.2 units/kg/day)²⁰. Other associated benefits of early mobilization include improved cognitive function¹⁶, improved functional exercise capacity, and improved self-perceived functional status at discharge²¹.

Early mobilization has been incorporated into many critical care settings, but due to limited physical therapists and occupational therapists, time constraints, inadequate staff training, and lack of staff support²², outside of the research realm, it has been a challenge to implement an early mobilization protocol. There have also been lingering concerns regarding safety, despite evidence supporting safe mobilization of even mechanically ventilated critically ill adults²³.

Nutritional Support During Critical Illness and Its Metabolic Consequence

Another contributing factor to hyperglycemia in ICU patients is nutrition. While it seems intuitive that enteral nutritional support would have a positive impact during critical illness, how best to deliver it is less well studied. Prior studies have already shown that enteral nutrition (EN) can preserve intestinal microbial diversity²⁴ and maintain gastrointestinal (GI) tract mucosal integrity²⁵ compared to parenteral nutrition (PN). However, very few studies have examined when and how to deliver that nutritional content, and without much evidence to support the practice, continuous provision (24 hours a day) of EN has become the norm. This practice, however, may have unintended consequences. Continuous uninterrupted 24 hour infusion of ‘food’ does not mimic the natural progression of eating a meal and the subsequent release of digestive enzymes and hormones. After meal consumption for example, serum glucose levels increase, leading to a release of insulin as well as the down-regulation of glucagon. The enterohormonal feedback loop is tightly regulated and highly preserved across species. After a meal, GI hormones rapidly rise and then return to basal levels. This cycle of rise and fall of hormone levels is interrupted by continuous tube feeding¹. When nutrition is constantly running through the digestive tract, insulin is constantly being released basally and the post-prandial surge is lost. There may even be a downregulation of insulin receptors over time. Downstream, this may be promoting an insulin resistant state and contributing to hyperglycemia. In an average day outside of the hospital, a patient is not eating continuously all day, but would likely consume about three meals a day and a few snacks in between. If it were possible to mimic these meal times with boluses of food instead of

a continuous infusion, patients may be able to maintain a more physiologic hormonal state.

Statement of the Problem

Currently, providers are attempting to balance the benefit of hyperglycemia treatment via exogenous insulin administration with the risk of hypoglycemia by adopting a less stringent glucose goal. The most recent recommendations from the American College of Physicians suggest a target blood glucose level between 140-200mg/dL among SICU/MICU patients²⁶. While immobilization and nutrition are contributors to hyperglycemia in the ICU, it is unknown how these factors may be intervened upon as adjunctive therapy beyond traditional insulin administration in an effort to more holistically manage glucose control during critical illness. Such non-insulin dependent management tools may have the additional benefit of less ‘cost’ in terms of severe hypoglycemia.

Goals and Objectives

The goal of this study is to examine whether implementation of a bundled supportive care regimen which includes a) an early and aggressive ICU mobilization program and b) intermittent bolus EN, could be a safe and feasible adjunct therapies for hyperglycemia in the critically ill patient using a 2 x 2 factorial design. Glycemic control metrics (such as average glucose levels, insulin requirements, peak and nadir glucose levels) will be examined among 4 groups of patients: (1) those who receive standard mobilization and continuous (24 hours a day) EN; (2) those who received standard mobilization and intermittent bolus (meals and snacks) EN; (3) those who receive

aggressive ICU mobilization and continuous (24 hours a day) EN; and (4) those who receive aggressive ICU mobilization and intermittent bolus (meals and snacks) EN.

Hypothesis

We hypothesize that an aggressive early mobilization protocol paired with an EN protocol utilizing intermittent bolus feeds will together decrease the amount of insulin units needed to treat hyperglycemia in critically ill patients in the ICU, compared to those receiving standard mobilization and continuous enteral nutrition.

Definitions

Hyperglycemia: fasting blood glucose $\geq 126\text{mg/dL}$ or a random blood glucose $>200\text{mg/dL}$

Hypoglycemia: blood glucose $<40\text{mg/dL}$

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Chapter 2 – Review of the Literature

Introduction

In this chapter, we will present a comprehensive literature review to summarize, compare and contrast, and critically evaluate previous research on this topic. This review of the literature between August 1980 and July 2017 was conducted using PubMed@Yale, OVID (Medline and Embase), Scopus, and Cochrane databases. Keywords used to find the necessary articles to conduct the literature review included those in Table 1 below. Applicable articles were limited to those written in or translated to English. Systematic review articles, randomized controlled trials, prospective and retrospective studies as well as relevant referenced articles were all used to complete the literature review necessary to validate this proposed study.

Table 1. Literature Search Key Terms

Critical Illness / Critically Ill / Intensive Care Unit / Critical Care
Early Ambulation / Movement / Mobilization
Hyperglycemia
Enteral Nutrition

Review of Empirical Studies Regarding Mobilization

Early and aggressive mobilization has been shown to have beneficial effects on critically ill patients¹⁻³. Burtin et al. performed a randomized controlled trial in a medical and surgical ICU at an academic institution with 90 critically ill patients¹. While both the control and intervention groups received respiratory PT and daily standardized passive or active range of motions session of upper and lower limbs, the intervention group also received daily passive or active exercise training using a bedside ergometer for 20 minutes starting from day 5 of the ICU stay once cardiorespiratory status was felt to be

sufficiently stabilized. While there was no difference with regard to quadriceps force and functional status between the control and intervention groups, six minute walking distance, isometric quadriceps force, and subjective feeling of functional well-being (per a validated health survey) were all significantly higher in the intervention group ($p < 0.05$) at time of hospital discharge. No adverse events related to mobilization occurred in this study. This was one of the earlier studies that suggested benefit and feasibility of early exercise amongst ICU patients and informed subsequent studies.

In 2013, Engel et al. examined the implementation of an ICU early mobility quality improvement initiative from three separate institutions, which included the MICU at Wake Forest University (WFU), the MICU at Johns Hopkins Hospital (JHH), and the mixed surgical-medical ICU at University of California San Francisco Medical Center (UCSF)³. All three institutions found reduced ICU and hospital length of stay (LOS) as well as improved outcomes and saved costs. For example, at WFU there was a significant difference in ICU LOS between usual care (6.8 days) in comparison to the protocol group (5.5 days) as well as a significant difference in overall hospital LOS (14.5 days in usual care versus 11.2 days in protocol group). They also found a net savings of over a half a million dollars of total direct inpatient cost in the protocol group. JHH and UCSF had similar results. The program at JHH additionally found decreased rates of delirium and need for sedation. All three of the locations required an interprofessional team-based approach to plan, educate, and implement the early mobilization program including but not limited to physical therapists, occupational therapists, physical medicine, critical care providers, neurology providers, clinical and nursing staff. At a certain point in the implementation, UCSF found themselves in a shortage of staffing to maintain the

protocol. While safe, feasible, and beneficial for a wide range of critically ill patients, Engel's study highlighted implementation challenges related to early mobilization which ranged from infrastructure resource needs to multidisciplinary stakeholder buy-in.

We are thus left with a disconnect—while research evidence has continued to accumulate that early mobilization is beneficial among ICU patients, the bedside reality is that early mobilization is frequently not occurring to the extent that it can or should. Upon investigation into the current state of ICU mobilization, the Trial of Early Activity and Mobilization (TEAM) Study investigators found in their multi-center, prospective cohort study that early mobilization of mechanically ventilated patients was uncommon⁴. In 12 ICUs across Australia and New Zealand between August 2012 and March 2013, 192 patients who were previously functionally independent and expected to be ventilated for greater than 48 hours were followed for 14 days or until liberated from the ventilator, whichever came first. Results demonstrated that 122 patients (63.5%) did not receive early mobilization. Of the possible 1288 patient-PT interactions while patients were mechanically ventilated, no early mobilization occurred in 1079 (84%) of these episodes. Of the 36.5% mechanically ventilated patients who did receive any active mobilization, less than 10% of mobilization episodes included any activities out of bed. For these patients, the median time from ICU admission to mobilization was 5 days and the number of active mobilization episodes per patient was 2. Strengths of this study include its prospective multicenter design as well as the fact that it took place in Australia and New Zealand where PT has been part of the ICU multidisciplinary team for decades⁴. However, patient follow-up was limited to 14 days which is a shortcoming given that

recovery from critical illness as well as the known benefits of mobilization may persist past 14 days.

With proven benefit of mobilization but real world evidence that early mobilization is not being implemented, what are the barriers? In their review, Dubb et al. examined these unique barriers to early mobility in the ICU setting which are outlined below in Table 2⁵.

Table 2. Barriers to Early Mobilization⁵

Physical barriers	Patients considered too sick Hemodynamic instability Arrhythmias Respiratory instability Pain Poor nutrition status Obesity Baseline or new immobility or weakness
Neuropsychological barriers	Sedation Paralysis Delirium Agitation Lack of motivation Anxiety Fatigue Palliative care
ICU devices and equipment	Hemodynamic monitoring equipment Lines Tubes Drains
Cultural barriers	Inadequate staff Lack of staff buy-in Lack of multidisciplinary culture Lack of patient/family knowledge
Process related barriers	Lack of planning and coordination Unclear expectations, roles, responsibilities Missed/delayed screening for ability Standing orders for bed-rest Risks for mobility providers (stress/injuries)

Meanwhile, additional benefits of early mobilization are being discovered. A secondary analysis of a previous randomized controlled trial of early PT/occupational therapy (OT) versus conventional therapy is one example where metabolic benefits to early mobilization were suggested⁶. In the original study, 104 MICU patients were randomized to receive PT/OT within 72 hours of mechanical ventilation (early) or standard care as ordered by primary team⁷. As with other studies, patients randomized to more intensive and early PT were shown to have improved functional independence at time of discharge. As part of the study, total daily insulin dose was collected during ICU stay and normalized to weight, and the outcome variables were measured as medians⁶. After a univariate analysis, this study established that the mobilized patients required less insulin (0.07 units/kg/d versus 0.2 units/kg/d, $P < 0.0001$). This was remarkable given a slight and non-significant trend toward more prednisone dosage in the early mobilization patients. This study was unique in that it suggested that early mobilization may have potential utility as adjunct to insulin to improve metabolic parameters during critical illness. This study focused on MICU patients, eliminating the possible heterogeneity and varying co-morbid conditions that may otherwise exist with inclusion of surgical patients or patients with neurologic injury. Conversely, the focus on MICU patients limits its generalizability. This study took place during the era of IIT (in this study, targeting a blood glucose of 80-120 mg/dL) so approach to glycemic control was standardized. Patients in the MICU receive corticosteroids for various indications, such as for obstructive lung disease and relative adrenal insufficiency that can occur during severe septic shock. While receipt of corticosteroid was not statistically significant between groups, there was a trend toward more usage among patients in the early mobilization

arm, which may have been due to incomplete randomization. However, this could have biased the early mobilization group to need more (not less) insulin, and thus may in fact strengthen the study findings. Finally, given that this was a secondary analysis of a prior study, it may not have been appropriately powered to examine the metabolic impact of mobilization on hyperglycemia.

Nevertheless, mechanistically, the effects of immobilization on blood glucose have been known. In the study by Stuart et al. from 1988, investigators aimed to quantify the impact of absolute bed-rest alone on the insulin regulation of glucose metabolism⁸. Six healthy men aged 21 to 28 years old were admitted and had baseline testing. On the sixth day of admission bed-rest was begun, and patients were confined to a water bed for seven days and not permitted to deviate from a recumbent position. Glucose tolerance tests were performed on day 4 (during the baseline period) and day 11 (during the sixth day of bed-rest). Results of this study showed an increase in plasma glucagon and urinary free cortisol, both of which are insulin antagonists. While fasting glucose was unchanged by bed-rest, post-prandial challenge glucose levels tended to be elevated ($p < 0.05$) and the insulin area of the glucose tolerance test was increased by 44% ($p < 0.01$). The slight rise in glucose with a moderate increase in insulin secretion suggests the development of insulin resistance within a week of bed-rest among healthy volunteers. Given that there are many other factors such as increase in counter-regulatory hormones during stress states in the ICU, bedbound critically ill patients may thus be primed to experience hyperglycemia.

Reassuringly, even short and limited exercise may help ameliorate this insulin resistant state. In one study, Devlin demonstrated that a single bout of exercise in non-

insulin dependent diabetic men can increase peripheral and splanchnic insulin sensitivity for the subsequent 12-16 hours⁹.

Review of Empirical Studies Regarding Treatment of Hyperglycemia in the ICU

As discussed in Chapter 1, stress hyperglycemia often occurs in critical illness and can have a negative impact on recovery¹⁰⁻¹³. How to best manage hyperglycemia during critical illness has been a topic of great controversy in the past decade.

In 2001, Van den Berghe et al. performed a prospective randomized controlled trial looking at whether complete normalization of blood glucose levels with IIT reduces mortality and morbidity among critically ill patients¹⁴. The study included 1548 adults admitted to a SICU receiving mechanical ventilation. The intervention arm received IIT with a target blood glucose of 80-110mg/dL whereas the conventional treatment had insulin management with a target blood glucose of 180-200mg/dL. The study was originally powered to detect a 5% difference in mortality among those who remained in the ICU for more than five days and of 3% among all patients in the ICU. Interim analysis of results indicated that conventional treatment was inferior, and the study was stopped prior to the planned 2500 enrollment. Results demonstrated that IIT reduced mortality during ICU stay from 8% in the conventional group to 4.6% ($p<0.04$). In patients who remained in the ICU for greater than five days, the mortality rate with IIT was 10.6% compared with 20.2% in the conventional group ($p=0.005$). The sickest patients appeared to reap the most benefit, as the largest reduction in mortality was observed in deaths due to multi-organ failure, particularly those with septic shock. Results also indicated IIT was associated with an overall reduction in hospital mortality by 34%, and marked improvement in clinically relevant morbidity markers such as

reduction of rates of bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, median number of red cell transfusions by 50%, and critical-illness polyneuropathy by 44%. Patients in the IIT arm of the study were less likely to require prolonged mechanical ventilation and intensive care. One of the biggest strengths of this study was a novel aggressive treatment approach (using a widely available and cheap drug—insulin) to a known and ubiquitous problem of stress hyperglycemia during critical illness. Limitations of this study include that it took place exclusively in a SICU at one institution with a distinctive approach that emphasized the importance of glucose monitoring (utilizing point of care blood glucose measurements with arterial blood from an arterial catheter) and strict protocol adherence possibly limiting external validity and generalizability. Additionally, patients were supplemented with PN to meet caloric needs possibly increasing the insulin requirements.

In the subsequent years since the Van den Berghe trial, there have been many studies with conflicting data about the use of this IIT. These studies¹⁵⁻¹⁸, including the landmark NICE-SUGAR trial¹⁹, are discussed in Chapter 1. In their systematic review, Ling et al. looked at 22 randomized controlled trials comparing intensive glucose control (<110mg/dL) to conventional glucose control in adult intensive care patients²⁰. In this review, they used risk ratio (RR) as a summary measure of association with a 95% confidence interval. They performed a subgroup analysis on the mean blood glucose level achieved in the intensive group, the difference of mean blood glucose level achieved in the intensive and conventional control groups, the standard deviation (SD) of mean blood glucose (as an index of glycemic variability), the percentage of diabetic patients, the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score, the

percentage of medical patients, and the mean daily insulin dose in the intensive group. Results of this review showed that intensive glucose control did not significantly reduce short term mortality, reduce rates of sepsis, or reduce new need for dialysis. While the studies in separate medical or surgical ICUs showed no significant difference in long term (90 day or 180 day) mortality between the intensive and conventional groups, the intensive group had an increased risk of long term mortality compared with control in studies with mixed ICUs (RR = 1.10, 95% CI: 1.02-1.19, p=0.01). Additionally, the intensive control group had significantly increased risk of hypoglycemia (characterized as blood glucose <40 mg/dL) compared with the conventional group (RR=5.01, 95% CI: 3.45-7.28, p<0.00001). While these studies appear to conflict with the original Van den Berghe study, it should be noted that the original study compared this IIT with a blood glucose goal of 80-110mg/dL to the blood glucose standard of 180-200mg/dL. The majority of the subsequent studies compared IIT to a more moderate blood glucose (often <180mg/dL and most frequently in the 140-180mg/dL range¹⁹). Therefore, the mortality benefit in the original study may have been driven by avoiding excessive hyperglycemia during critical illness while subsequent studies showed that the approach may not need to be so 'intensive' to reap a benefit and additionally suggested the importance of avoiding severe hypoglycemia, which has its own consequences.

Given this, current guidelines from the American College of Physicians recommend not using IIT to strictly control (80-110mg/dL) blood glucose in SICU/MICU patients with and without diabetes mellitus²¹. Based on their extensive literature review through January 2011, many of the trials showed no effect on mortality and there was no trend toward overall benefit to this strict approach. Rather, IIT was

associated with excess risk for hypoglycemia in almost all trials. Current recommendations suggest a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200mg/dL) if insulin therapy is to be used in SICU/MICU patients.

As the discussion above shows, much of the focus to date regarding hyperglycemia management has been related to defining the appropriate target population as well as target blood glucose range utilizing insulin therapy. Very little work has been put forth examining non-insulin mechanisms to prevent hyperglycemia or ameliorate insulin resistance. As discussed in the prior section, immobilization during ICU stay can exacerbate hyperglycemia and in turn early and aggressive ICU mobilization may be an untapped adjunctive and holistic intervention to better manage hyperglycemia. Another area of inquiry relevant in that vein, pertains to EN in the ICU.

Review of Empirical Studies Regarding Enteral Nutrition

Glucose excursion is a known response to provision of EN. However, administration of continuous EN during illness, may cause unwanted and exaggerated hyperglycemia. For example in the prospective observational study by Pancorbo-Hidalgo and colleagues, 64 internal medicine patients fed by nasogastric (NG) tubes at a hospital in Spain were examined. Over one third of the patients were found to have hyperglycemia as a complication²². While EN has been shown to be the preferred method of artificial nutrition over PN, there has been little rigorous investigation to date defining how best to provide EN—for example, as intermittent bolus feeds versus continuous (24 hours a day). Currently, EN by continuous feeds are the status quo²³.

Few studies have explored how continuous versus intermittent feeds affects glucose. The limited that exist have been poorly designed with indistinct results and a

small sample size. In the study by Murphy et al., three different enteral feeding and insulin regimens were compared in a single hospital in the United Kingdom with the aim of improving glucose control and reducing hypoglycemia²⁴. Part of the study was done with a retrospective analysis of the hospital's current standard management of enteral feeds in diabetic patients (n=18) which involved 20 hour feeds with 30:70 premixed insulin. The second and third cohorts were analyzed prospectively. The first 13 eligible patients admitted were enrolled in the intermittent feed group and were administered three bolus feeds (4 hours each) with a basal bolus insulin regimen consisting of short acting insulin at each feed and long acting insulin at night. The next 15 consecutive eligible patients admitted were enrolled in the continuous feed group that incorporated 24 hour feeds with a long acting insulin analog 1-2 times per day. Results did not show a significant difference in overall glucose control or a difference in glucose variability between all three groups. No significant difference was found in glucose concentrations between the groups during feeds or fasting. It is hard to know whether there were sufficient differences in the intervention itself, for example between the 20 hour fed group versus the 24 hour fed group. The retrospective group receiving the current standard resulted in a high incidence of hypoglycemia and overall suboptimal glucose concentration. Of note, somewhat counterintuitively, there were significantly fewer episodes of hypoglycemia during the feeding period in the intermittent feed group ($p=0.006$). There was a high level of glucose variability across 24 hours in each group, but no significant difference in variability between groups. The design of this study is a significant limitation, as one third of the data were collected retrospectively while the rest was collected prospectively, limiting the ability to match all three groups. Given that this

study included only diabetic patients, it is not generalizable to non-diabetics. The study size was quite small, and likely without sufficient power to detect a difference.

Additionally, the small study size did not allow for control for potential confounders including severity of illness and concurrent infection. This was a small single center study and the majority of these patients had brain injury also leading to a lack of generalizability of the results. Several of the episodes of hypoglycemia (5 of 33 in the intermittent group, 2 of 24 in the continuous group, unable to be measured in standard as retrospective) were due to protocol violations which could be a concern for protocol adherence overall.

Another comparative study by Campbell et al. looked at glucose control with continuous EN versus EN with feeding breaks²⁵. This study included 20 ventilated patients in a seven bed combined medical and surgical ICU within a small district hospital. Enteral feeding was established after the third day of admission and data were collected for 48 hours. The control group received enteral feeding for 18 hours with 8 hour breaks, and the intervention group received continuous enteral feeding over 24 hours. The first 10 eligible patients were enrolled in the control group. Subsequent data collection was delayed a week allowing for adaptation of a new protocol before the next 10 eligible patients were enrolled in the intervention group. Data were analyzed through a non-parametric Mann-Whitney approach, and results showed continuous enteral feeding reduced blood glucose levels significantly ($p=0.005$) as well as improved blood glucose control and reduced insulin requirements. This study has several limitations. The generalizability could be questioned given the small sample size in a small district hospital with a combined medical and surgical ICU. Data were only collected for 48

hours, and as critical illness and the associated stress hyperglycemia can fluctuate and persist for days, this may not have reflected the longer term effects of the intervention. This also could pose a problem in ensuring adequate time to meet nutritional goals that could affect blood glucose levels. Additionally, representation of medical and surgical patients between the groups was different; four surgical patients were in the continuous enteral feeding group versus one surgical patient in the intermittent feeding group. Blood glucose control could vary according to diagnosis as well as surgical intervention. It is important to note that the intermittent intervention of this study is not the physiologic three meal approach that we are proposing but rather just an 8 hour break from the continuous feeds. This is actually similar to the group in the Murphy trial discussed above which resulted in a high incidence of hypoglycemia and overall suboptimal glucose concentration²⁴.

One additional study by Evans et al. was to determine if there was a difference in glycemic variability and insulin utilization in continuous tube feed (CTF) versus bolus tube feeds (BTF) in a prospective, randomized pilot study²⁶. Secondly, this study aimed to compare tube feed volume and caloric delivery as well as the incidence of hypoglycemia and the time needed to achieve >80% goal nutrition. From March 2012 to May 2014, in the surgical and neurological critical care units at a single institution, 50 patients were enrolled and randomized to receive either BTF or CTF after percutaneous endoscopic gastrostomy (PEG) placement. Per protocol at this institution, all patients were placed on an insulin sliding scale regimen administered every 6 hours for treatment of blood glucose greater than 120. The study was designed to detect a mean difference of 25% in primary endpoints (glycemic variability and insulin use) with power of 0.80 and

alpha <0.05. Results indicated that glycemic variability is not significantly affected by BTF versus CTF. The study also found that there was no significant difference in overall insulin utilization between the groups. No statistical differences were found in the secondary outcomes of median time to $\geq 80\%$ goal nutrition, tube feed interruptions, and incidence of hypoglycemia as well. A strength of this study is its randomization, which the prior studies discussed have not achieved. While another strength of this study is that there were no statistically significant differences in age, gender, APACHE II, and body mass index (BMI) between control and intervention groups, a flaw is that given the relative small size of this study, additional potential important confounders could not be accounted for such as baseline presence of or control of diabetes mellitus as well as any corticosteroid use²⁶. There was additionally a lack of strict inclusion/exclusion criteria based on diagnoses. Given its focus on PEG tube placement, the results lack external validity to patients with other enteral access methods (such as nasogastric or nasojejunal tube) or other healthcare settings. These studies by Murphy²⁴, Campbell²⁵, and Evans²⁶ are examples of the few studies examining intermittent versus continuous EN with inconsistent results and poor design.

While human studies have been limited, the physiologic impact of continuous versus intermittent EN have been highlighted by animal studies. Stoll and colleagues utilized 60 female neonatal pigs who were fed by intermittent EN with polymeric formula, intermittent EN with elemental diet, EN continuously, or PN continuously for 14 days²⁷. Investigators administered IV glucose tolerance tests on days 7 and 14 and hyperinsulinemic euglycemic clamps on day 14 and found that in continuous EN and PN, insulin secretion during glucose tolerance test was significantly higher ($p < 0.05$) and

glucose infusion rates during clamp were lower ($p<0.05$) than in the intermittent groups. These results indicate that when nutrition (PN and EN) is given continuously there is a reduction in insulin sensitivity. Given that this study took place in animals, human studies are needed to further characterize these changes.

The cyclic process of eating meals is a highly evolutionarily preserved process; it is not natural for our gastrointestinal (GI) tract or our endocrine system to receive nutrients continuously. Animal studies have shown that continuous nutrition induces GI tract atrophy as well as metabolic imbalance of key hormones that influence multiple organ systems²⁸. Mechanistic human studies have shown that continuous nutrition also negatively affects intestinal hormones and consequent gallbladder function^{29,30}. Apart from GI and endocrine studies, continuous nutrition also affects muscle synthesis, which in the ICU population is critically important as deconditioned and atrophied patients rehabilitate less well and portend a poorer prognosis³¹. Studies suggest that protein synthesis is less stimulated by continuous feeding versus intermittent feeding³². Finally, critical homeostatic mechanisms such as autophagy are interconnected with nutritional (fed-starved) cues and may impact recovery from critical illness³³. Continuous feeding approaches may completely abrogate this response.

While safety and tolerability is often cited to support continuous feeding as a gentler way to feed during illness, studies have shown that bolus feeds are tolerable. In the systematic review by Aguilera-Martinez et al.³⁴, they aimed to examine the existing literature regarding the effectiveness of continuous EN versus intermittent EN. Inclusion criteria for the review required the studies to have patients over 18 year old with a NG tube receiving EN in the ICU. Ultimately six studies fulfilled the criteria including

randomized controlled trials, clinical trials without randomization, and before and after studies. Investigators defined continuous EN as gravity administered or by feeding pump continuously for 12 or more hours per day. Intermittent EN was defined as nutrition administered by bolus, gravity, or feeding pump several times per day with rest between feeds. No studies found a significant difference in digestive intolerance between groups. One study found that intermittent EN had a lower risk of aspiration pneumonia with an odds ratio = 0.146 (95% CI = 0.062-0.413; $p = 0.000$). Despite two studies showing better nutritional results in less time and possibly reduced aspiration pneumonia risk with intermittent EN, ultimately there was not sufficient evidence in these studies to support continuous versus intermittent EN methods.

Given the lack of clear safety concerns and equipoise in terms of how optimally to provide nutritional support during critical illness, in the most recent 2016 guidelines, American Society for Parenteral and Enteral Nutrition (ASPEN) suggests intermittent bolus nutrition as one option²³. As intermittent bolus feeds are tolerable, safe and could be considered more physiologic than continuous feeds, as well as may impact blood glucose excursions during illness by normalizing enterohormonal feedback loops, it is likely that this could be another untapped, adjunctive intervention for the treatment of hyperglycemia in the ICU.

Review of Studies to Identify Possible Confounders

In this section, we will examine various confounding factors that may affect degree of hyperglycemia as well as the treatment but that will not be the primary focus of the proposed study.

Corticosteroids are well known to reduce insulin sensitivity in healthy individuals³⁵. In the critical care setting, glucocorticoids are widely used as treatment for a range of inflammatory and allergic disorders³⁶. There could be a concern that those critically ill patients treated with corticosteroids require higher insulin doses due to this insulin resistance. In order to control for this, the Evans study excluded patients that required corticosteroid use²⁶. Given that this exclusion criteria eliminates a large amount of ICU patients, this is not ideal. The majority of the other relevant studies discussed have utilized a multivariate analysis to see if there are significant differences between groups. On univariate analysis, we will ensure that a relative equal proportion of patients in each group has steroid exposure during ICU stay.

Another potential confounding variable is severity of disease. Do those who are sicker in the first place benefit from the intervention less than those who are healthier, or vice versa? One way that many studies have tried to acknowledge this confounder is a multivariate analysis adjusting for APACHE II scores^{6,17,19,25,37}. The APACHE II score provides a summative score based upon initial values (the most deranged parameter within the first 24 hours of ICU illness) of 12 routine physiologic measurements, age, and previous health status to provide a measure of severity of disease (Appendix A)³⁸. Combined with an accurate description of disease, this scale allows for the stratification by prognosis of acutely ill patients. Scores are from 0 to 71, and higher scores correlate with increased risk of hospital death. APACHE II is widely used and well validated among a heterogenous group of critically ill patients in the ICU and can be a useful tool to account for severity of illness in intervention studies.

Presenting diagnosis could also be considered a possible confounding variable. This is a common problem in ICU-related studies, particularly in the MICU where patients are heterogeneous. Several studies use a subgroup analysis by presenting diagnosis¹⁷. For example, the Campbell study comparing continuous versus bolus enteral feeding effects on blood glucose could be criticized for its that unequal representation of surgical and medical patients between the control and intervention²⁵. While limiting a study to an exclusively medical or surgical ICU can help control for this confounder, this limits a study's generalizability. Even the original Van den Berghe studies had slightly differing results in MICU³⁹ versus SICU¹⁴.

Analgesia and sedation are commonplace and often necessary in the ICU to provide comfort and safety to patients, especially those mechanically ventilated, but they can also lead to unexpected complications, prolonged mechanical ventilation, prolonged ICU LOS, and increased rates of delirium⁴⁰. One proven way to combat this is an approach with an emphasis on awakening and breathing trials, choice of appropriate sedation, delirium monitoring, early mobility and exercise (ABCDE approach)⁴¹. Despite proven approaches such as this, some ICU patients are still found over-sedated (more than is clinically necessary) which ultimately becomes an obstacle to early mobilization. Some studies have tried to overcome this by controlling for degree of sedation using the Richmond Agitation-Sedation Scale (RASS). This validated scale has established reliability between different raters in different healthcare positions (Appendix B)⁴². It has an ability to detect changes in sedation status over consecutive days of ICU care, against constructs of level of consciousness and delirium, and correlated with the administered dose of sedative and analgesic medications.

A final confounding variable relates to the way in which blood glucose is being measured and reported. In a 2005 study, investigators performed a comparison of glucose meter analysis of capillary blood (finger stick), glucose meter analysis of arterial blood, and blood gas/chemistry analysis of arterial blood in 30 consecutive adult medical and surgical ICU patients. Results demonstrated significantly better clinical agreement with the central lab for arterial samples (69.9% with glucose meter analysis and 76.5% with blood gas/chemistry analysis) in comparison with the finger sticks (56.8%). With episodes of hypoglycemia, overall clinical agreement was <70% and finger stick was as low as 26.3%⁴³. These differences led to disagreements over treatment dose and titration of insulin for hyperglycemia.

Ultimately, randomization should aide to control for these confounders. With randomization, patients have equal chance to be assigned to intervention or control, thus minimizing differences among groups by theoretically distributing people with particular characteristics among groups.

Review of Relevant Methodology

In this section, we will review the methodology of prior studies relevant to the proposed study and justify our methodology.

Study Design

While there have been a significant number of randomized controlled trials examining the use of insulin for the treatment of hyperglycemia in the ICU^{14,16-18,44}, there have been very few studies examining adjunctive therapies that focus on non-insulin based approaches. The most convincing data for the benefit of early mobilization in hyperglycemia is from a secondary analysis of a previous study that may not have been

appropriately powered to examine those benefits⁶. A randomized controlled trial is needed to explore its role in reducing the insulin requirements.

Continuous versus intermittent bolus EN have been compared in a few studies with no conclusive outcome. While animal studies have indicated benefit of intermittent bolus feeds in reducing insulin resistance²⁷, human studies are limited and a randomized controlled trial is necessary to observe this impact. Although they only looked at patients with PEG tubes, Evans et al. had a well-designed randomized controlled trial²⁶.

Randomized controlled trials help to prevent selection bias and decrease the probability of confounders. Given the benefits of a randomized controlled trial, the design of previous studies, and the current equipoise regarding our interventions, this proposed study will be a dual center randomized controlled trial using a 2 x 2 factorial design to take place over a two year period.

Inclusion and Exclusion Criteria

Among the studies discussed in this chapter, inclusion and exclusion criteria has varied. A majority of the studies included mechanically ventilated ICU patients over the age of 18^{4,7,26,45}. Regarding mobilization, several studies required patients to have baseline functional independence prior to admission^{4,7}. Several studies excluded patients with injuries that may preclude mobilization like unstable spine or pelvis injury as well as those patients for whom death appears imminent or unstable^{1,4,45}. Burtin and colleagues had extensive exclusion criteria such as conditions impairing movement (open abdominal wounds, extreme obesity defined as a BMI >35, serious bedsore or venous ulcers), body length <1.5m, preexisting diagnosis causing neuromuscular weakness, acute stroke, status epilepticus, coagulation disorders (INR >1.5 or platelets <50,000/mm³), and intracranial

pressure >20mmHg¹. Schweickert et al. excluded patients with active GI bleeds, and active myocardial infarction, or an unsecure airway, as well as patients with raised intracranial pressure⁷. Patients have been excluded who were unable to follow simple verbal commands in English⁴⁵ or if there was a prior history of cognitive impairment⁴ or dementia⁴⁵. The primary ICU providers were also typically given the option to exclude their patient if in their opinion, it was felt to be unsafe to mobilize the patient⁴⁵. Some studies excluded the patient for clinical instability, but what qualifies as being too unstable varies. For example, in one study, instability was defined by mean arterial pressure <65 or >110mmHg, systolic blood pressure >200, heart rate <40 or >130 beats per minute, respiratory rate <5 or >40 breaths per minute, or pulse oximetry <88%⁷ whereas in another study, instability was defined as fraction of inspired oxygen>55%, partial pressure of oxygen in the arterial blood <65, minute ventilation >150 mL/body weight, respiratory rate >30 breaths per minute, need for significant vasopressive support¹.

Regarding the nutritional component, Murphy et al. required patients to have normal GI function and to be receiving full nutritional needs by EN²⁴. Campbell and colleagues excluded patients receiving medications by mouth requiring feed breaks²⁵. Evans et al. excluded patients with any contraindication to enteral feeding as well as pregnant patients or those with prisoner status²⁶. Patients have been excluded from EN related studies for intestinal fistula, obstruction, necrosis, or peritonitis⁴⁶.

Typical exclusion for those included in studies for ICU related hyperglycemia included those who developed diabetic ketoacidosis or hyperosmolar state, which would

then necessitate a different protocolized approach for that hyperglycemic emergency state¹⁹. Per ASPEN guidelines, EN should be held for esophageal or gastric dysmotility²³.

Intervention

One of our goal interventions is aggressive and early mobilization such as that seen in the Schweickert study⁷ and that implemented at the three academic institutions in the Engel paper³. The paired and second distinct intervention is an intermittent bolus nutrition protocol similar to that in the Evans and Murphy studies, simulating three meals^{24,26}. This approach is unique compared to prior studies that have simply instituted a feeding break intervention such as 18hours continuous feeds with an 8 hour break²⁵.

Primary and Secondary Outcome Measures

Studies looking at insulin alone as the treatment for hyperglycemia have looked at various primary outcomes including death from any cause during intensive care^{14,16}, death from any cause in the hospital³⁹, and death from any cause within 90 days^{15,19}. The Evans study used primary endpoints of glycemic variability (defined as the difference between maximum and minimum value) as well as insulin utilization²⁶. Given that we are looking at therapy for hyperglycemia in the ICU that will be an adjunct to insulin, it is logical that we will examine a primary outcome similar to that measured in the Patel study—median total daily insulin dose normalized to weight (units/kg/day)⁶.

We will also examine some of the secondary outcomes measured in the trials discussed throughout this chapter. Several studies looked at secondary outcomes of ICU LOS^{12,13,20,45}, hospital LOS^{16,24,45}, ICU mortality^{7,16,17,45}, 90 day mortality^{4,17,19}, delirium days⁷, ventilator free days^{7,45}, as well as serious adverse effects (including falls, cardiac arrest, rapid or new onset atrial fibrillation, ventricular tachycardia, oxygen saturation

<80% for >3min, unplanned extubation, loss of invasively inserted line^{4,20,45}). An important secondary outcome to be measured is hypoglycemia defined as <40 mg/dL^{17,19,20}.

Sample Size

As this is a unique proposal for adjunct therapy of hyperglycemia in critically ill patients and there are no prior studies that we can utilize for a precise determination of our sample size, to estimate, we must extrapolate from studies that justify our rationale and primary hypothesis. For example, the Campbell study had a similar study population of critically ill patients as well as an outcome measure of insulin dose. Comparing continuous versus intermittent EN in 20 critically ill patients, their data demonstrated an effect size of 2.4mL/hour versus 3.2mL/hour with a standard deviation of about 1.7. Utilizing a sample size calculator with this data, a power of 80, α of 0.05, the goal sample size for each arm of the study was determined to be 71, leading to a total sample size of 284.

Conclusion

In this chapter, we have discussed numerous studies related to mobilization, treatment of stress hyperglycemia, and EN. Immobilization and EN have been shown to have a clear role in stress hyperglycemia in critically ill patients. Given controversy over the best treatment for this hyperglycemia, a study is needed to examine how EN and mobilization can be utilized in this area. Through our discussion of the methods of these studies, we have shown the rationale for our methods to be discussed in the next chapter.

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Chapter 3 – Study Methods

Study Design

This proposed study is a dual center randomized controlled trial designed to determine the effects of an early mobilization program and/or intermittent bolus EN upon glycemic control in the MICU utilizing a 2 by 2 factorial design.

Study Population and Sampling

Eligible patients will be selected from two campuses within Yale New Haven Hospital. Adult patients aged 18 and greater who are admitted to the MICU at either York Street Campus (YSC) or Saint Raphael Campus (SRC) will be screened for eligibility. Yale New Haven Hospital is a 1500 bed tertiary care academic hospital. Patients who present to the emergency department at either campus can theoretically be admitted to the MICU at either location, dependent on bed availability. There are some caveats: where a bed is available at either campus, patients are kept at the campus where they present to minimize movement. Additionally, patients with certain disease processes are preferentially admitted to the YSC (such as patients undergoing liver transplant or patients with malignancy particularly if they are already cared for at the Smilow Cancer Center). Acuity of illness is otherwise similar.

Inclusion criteria, as outlined in Table 2, will consist of mechanically ventilated males or females in the MICU over 18 years of age who are unable to ingest an oral diet but who have conserved GI function as well as baseline functional independence.

Exclusion criteria, as detailed in Table 3, consists of those without enteral access, with a history of gastric bypass (or any surgery that may restrict stomach distension), with a history of significant esophageal dysmotility who would be at risk of aspiration, those

who cannot have their head elevated at least 30 degrees while intubated and being fed per standard protocol (such as those with elevated intracranial pressure), those chronically fed via a percutaneous gastric tube, those with a nasojejun tube, those who are pregnant, those receiving infusions of neuromuscular blockade, and those with a hyperglycemic emergency (diabetic ketoacidosis or hyperglycemic hyperosmolar non-ketotic coma) as well as any those with any contraindication to enteral diet such as intestinal fistula, obstruction, necrosis, peritonitis. Additional exclusion criteria are injuries that may require immobilization (such as unstable spine or pelvic fracture), increased intracranial pressure, active GI bleed, active myocardial infarction, cognitive impairment, dementia, or unable to follow simple English commands.

Table 3. Inclusion Criteria

INCLUSION CRITERIA
Over 18 years of age
Admission to York Street Campus or St. Raphael's Campus MICU
Mechanical Ventilation
Preserved GI function
Baseline functional independence

Table 4. Exclusion Criteria

EXCLUSION CRITERIA
Without enteral access
History gastric bypass (or any other surgeries that may restrict stomach distension)
History of esophageal dysmotility
Unable to have head of bed elevated at least 30 degrees while intubated and being fed per standard protocol
Chronically fed enterally via percutaneous gastric tube
Nasoejunal tube
Pregnant
Receiving infusions or neuromuscular blockade
Hyperglycemic emergency (diabetic ketoacidosis, hyperglycemic hyperosmolar non-ketotic coma)
Injuries that preclude mobilization
Increased intracranial pressure
Active GI bleed
Active myocardial infarction

Cognitive impairment
Dementia
Unable to follow simple commands

Subject Protection and Confidentiality

As either intervention is minimal risk with no significant alteration from current ICU practice that is offered as part of bundled supportive care for all patients, a waiver of informed consent will be obtained through the local institutional review board (IRB). We will collect data on all eligible patients.

The study will be in compliance with HIPAA regulations, and patient confidentiality will be maintained throughout the study. Research data will be stored on a secure network. Per Yale research regulations, all participants will be de-identified, and identifiers and the means to link the names and codes will be stored in separate locations in the database per IRB protocol. A data and safety monitoring board will intermittently check the accruing data for benefits and harm and monitor for adverse events. This board will have the capability to terminate the study at any point if they have concerns about safety.

Recruitment

Consecutive patients who are admitted to the MICU who meet inclusion criteria will be included for analysis. This might include patients who are economically disadvantaged, decisionally impaired, employees or students who are admitted to the MICU, as well as women of reproductive age. There will be no exclusions made on the basis of gender, race, ethnic, economic or educational background. Vulnerable patients will not be specifically targeted or recruited for this study. Research staff will screen patients upon admission to the MICU on a daily basis. All patients will be included

consecutively once a determination is made by the primary treatment team to initiate nutritional support (typically within 24-48 hours of ICU admission as part of standard ICU supportive care) based on the usual clinical criteria. If an eligible patient is admitted and enrolled in the study, the ICU dietician will provide specific recommendations for continuous or intermittent bolus feeding dependent on randomization. The team will be notified of patient inclusion and will have an opportunity to decline participation if they feel there are unique factors that make the patient less suitable. Enrollment will be continuous until the goal patient enrollment number is met.

MICU nursing staff, pharmacists, and providers will be notified of this study initiative prior to the start date and will be provided information about the relevant background and will be given a detailed standard operating procedure (SOP). The nursing staff will be intimately involved in the execution of the feeding intervention as they routinely administer EN in the ICU, and a frequently asked questions/SOP pamphlet will be provided (Appendix C). There will be ample opportunity to discuss concerns and questions. Nursing staff will be offered in-service sessions by the ICU dieticians and research team.

Study Variables and Measures

In the control arm, patients randomized will receive ad lib mobilization as ordered by the primary team and will be given continuous EN. In the intervention arm, patients will undergo rigorous early mobilization as well as a bolus EN protocol that simulates three meals and three snacks a day with no feeding period at night during sleep.

The primary outcome of interest in this study will be degree of glycemic control defined by the number of insulin units (units/kg/day) required to treat hyperglycemia as

well as average blood glucose per hospital day. Additionally, this study will examine the secondary outcomes of ICU LOS, hospital LOS, ICU mortality, hospital mortality, delirium days, and other complications that may occur related to the intervention (such as, hypoglycemia, infection, aspiration, abdominal distension, number of patients who could not tolerate intermittent bolus meal and who were crosses over to continuous).

Intervention

With regard to the early mobilization intervention, state of the art early and aggressive PT/OT will be compared to ad lib PT/OT as ordered by primary team. At YSC, dedicated PT/OT staff has been secured specifically for the MICU for the last several years, allowing therapy 7 days a week with allocated resources to serve this population. Thus, patients admitted to the YSC will be automatically assigned to the aggressive mobilization intervention. At SRC, to date such resource arrangements have not yet been made, and PT/OT is ordered and administered ad lib according to resource availability.

For the nutrition intervention of the study, within 24 hours of admission to the MICU on either campus, patients will be randomly assigned to receive continuous enteral feeds or an intermittent bolus feeding protocol which will simulate three meals and three snacks a day. The actual timing of feeding initiation will be left to the discretion of the primary team.

Blinding of intervention

The allocation of patients for the two mobilization interventions depends on the hospital at which the patient is being treated. Thus, it will not be possible to blind the mobilization component of this study. For the nutrition intervention, treatment

assignments will be concealed before randomization, but due to the nature of the intervention, it will not be possible to blind care staff or patient.

Adherence

We will track PT/OT sessions in both groups to ensure that there is a sufficient difference between the arms of the study. The number of sessions a week, the number of minutes per session, the type of mobilization attempted, as well as patient progress will be followed. Both campuses utilize the electronic medical record system EPIC. In EPIC, templates will be created that will be filled out by the therapist after each session indicating the time and exercises performed with each patient. For the nutrition intervention, we will monitor calories per day, skipped meals or snacks as well as reason for being skipped (e.g. for a test, for intolerance, etc.), and number of hours fed per day for continuous infusion in a template form to be filled out by nursing staff.

Data Collection

Data will be continuously collected throughout the inpatient admission. Baseline data will be collected at the time of admission to allow for comparison of participant characteristics in each of the study groups. This data will include age, sex, BMI, baseline functional status, admitting diagnosis, APACHE II score, presence of sepsis, pre-existing diagnosis of diabetes mellitus, and use of concomitant therapies such as mechanical ventilation, renal replacement therapy, and corticosteroids.

Blood glucose will be monitored and managed with insulin treatment according to the existing ICU hyperglycemia protocol (Appendix D). From the time of randomization to the time of discharge from the ICU or 90 days after randomization (whichever comes first) all blood glucose measurements, insulin administration, red cell administration,

positive blood cultures, volume of all EN, additional IV glucose administration, and corticosteroid administration will be recorded in EPIC. Aside from the timing of how EN and PT/OT will be administered, all other aspects of patient care will be carried out as appropriate by the treating physicians according to unit standards. Trial intervention with regard to nutrition will be discontinued once the patient is eating by mouth. For mobilization therapy, this will be continued until ICU discharge. Patients readmitted to the ICU during the same hospital encounter will be re-enrolled and assigned a different study number. Study participants will be followed until death or hospital discharge.

Sample Size Calculation

We will be using two-sided hypothesis testing with an alpha of 5%, a beta of 20% and a power of 80%. Using sample size calculator as discussed in Chapter 2, this leads to an unadjusted sample size of 71 patients in each arm, totaling 284 in the study.

(Appendix E)

Analysis

The primary endpoint of median units of insulin used (units/kg/day) will be evaluated using a Kruskal-Wallis analysis. Kruskal-Wallis analysis will also be performed for the other continuous secondary outcomes (ICU LOS, hospital LOS, delirium days, ventilator free days). We will be using ANCOVA testing for further multivariate analysis controlling for potential confounding variables such as gender, race, age, severity of illness (APACHE II scores), organ failure scores, and caloric intake. The other secondary outcomes, both dichotomous and nominal, will be evaluated using a chi square test.

As we anticipate that these targeted interventions will be most beneficial for patients who remain in the ICU for greater than 3 days, a priori, the primary analysis of interest will focus on comparing the impact of the dual interventions between those in the ICU for greater than 3 days versus not. An intention to treat whole group analysis will also be performed as a secondary analysis.

Timeline and Resources

Patients will be continuously enrolled from September 2017 until June 2019 or sooner if a total of 284 patients are reached. Funding will be provided per the Yale School of Medicine. Staff will include co-principal investigators Caroline Argyros, PA-S and Shyoko Honiden, MD as well as a study coordinator and research assistants. This study will require the support of much of the MICU staff at both hospital campuses including medical providers, PT, OT, dieticians, and nurses.

Chapter 4 – Conclusion

Strengths and Limitations

This is a novel study investigating the efficacy of a non-insulin dependent multidimensional approach to the treatment of hyperglycemia among critically ill patients. The study focuses on supportive care already being provided in ICUs—EN and aggressive ICU mobilization. This holistic approach has the added benefit of minimizing severe hypoglycemia (blood glucose <40mg/dL) which has been the unavoidable ‘price’ paid in all prior studies which have investigated IIT. The randomized controlled trial design of this study allows demonstration of treatment effect more robustly than prior studies^{1,2}. The strict inclusion and exclusion criteria should minimize risk to patients and help identify patients who are most likely to benefit (and be eligible) for our suggested approach in the real world. Additionally, as all outcomes will be measured while patients are in the hospital, no issues should occur with data collection, adherence, or loss to follow up. The study variables are well-defined and set data collection procedures are in place that should ideally prevent information bias. Another strength of this study is that the mobilization component utilizes a system already in place—comparing the differences in the aggressive early mobilization that should be occurring at YSC versus the ad lib mobilization occurring currently at SRC—making execution of the study practical in a reasonable timeframe. We hope that leveraging the existing realities in the 2 study sites should also increase generalizability to a larger audience.

Despite the many advantages, there are a few notable limitations. It is a resource intensive study requiring the coordination of a multidisciplinary team which many prior studies have identified as difficult to implement³. Both of these protocols require

significant buy-in from staff which include dietitians, providers, nursing, as well as physical therapists. EN protocol is mostly nursing driven, and physical and occupational therapists are most integral to the mobilization component. Studies that take place in MICUs are classically plagued by the inherent heterogeneity of the patient population. Given that the mobilization arms are assigned based on which of the 2 study sites the patient is admitted to, it is possible that one site may see a larger proportion of certain diagnoses than others. However, we feel that the level of care provided is similar as providers go to both sites. Additionally ICU metrics and protocols used are the same between the sites minimizing bias. Severity of illness will be accounted for by the APACHE II score. Given the nature of both of these interventions, it is not possible for the clinician or patient to be blinded to the intervention or outcome. While administration of EN is a mostly patient independent process, mobilization requires patient participation and motivation. There could be an influence on outcome between patients who are more highly motivated or who have nurse or family members that encourage or allow for additional mobilization outside designated PT/OT sessions. It is important to be aware that early mobilization may in fact favor those patients that are destined to do well⁴ especially when looking at the secondary outcomes of ICU and hospital mortality.

While this study is limited in that it will not include any surgical or neurologic ICU patients, results of this study should be generalizable to most MICUs. Furthermore, the current study takes place at a large academic institution with significant resources. It may not be generalizable to smaller, more resource-limited hospitals—the biggest barrier would be the PT/OT staffing needs to maintain an early and aggressive mobilization protocol.

Clinical Significance

Treatment of stress hyperglycemia in the critically ill patient has been a source of controversy for over a decade. To date, insulin has been the primary and sole treatment that has been extensively examined. Given the narrow therapeutic index of insulin¹, finding the ideal target range for blood glucose has proven difficult. Given the implications of immobilization and EN on hyperglycemia, these would be ideal sources of intervention for a more physiologic and holistic approach to hyperglycemia versus a solely pharmacologic approach. Thus, this could lead to the incorporation of a bundled supportive care model utilizing EN and mobilization as treatment of hyperglycemia with a decreased risk of hypoglycemia in the ICU.

References

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Appendices

APPENDIX A: ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORE ¹

The APACHE II Severity of Disease Classification System

Physiologic Variable	+4		+3		+2		+1		0		+1		+2		+3		+4	
Temperature - rectal (°C)	≥41		39-40.9				38.5-38.9		36-38.4		34-35.9		32-33.9		30-31.9		≤29.9	
Mean Arterial Pressure (mm Hg)	≥160		130-159		110-129				70-109				50-69				≤49	
Heart Rate	≥180		140-179		110-139				70-109				55-69		40-54		≤39	
Respiratory Rate (nonventilated or ventilated)	≥50		35-49				25-34		12-24		10-11		6-9				≤5	
Oxygenation (mmHg) a. FiO ₂ > 0.5 use A-aDO ₂ b. FiO ₂ < 0.5 use PaO ₂	a	≥500	350-499		200-349				<200									
	b							> 70		61-70				55-60		<55		
Arterial pH	≥7.7		7.6-7.69				7.5-7.59		7.33-7.49				7.25-7.32		7.15-7.24		<7.15	
Serum Sodium (mmol/l)	≥180		160-179		155-159		150-154		130-149				120-129		111-119		≤110	
Serum Potassium (mmol/l)	≥7		6-6.9				5.5-5.9		3.5-5.4		3-3.4		2.5-2.9				<2.5	
Serum Creatinine (mg/dl, Double point score for acute renal failure)	≥3.5		2-3.4		1.5-1.9				0.6-1.4				<0.6					
Hematocrit (%)	≥60				50-59.9		46-49.9		30-45.9				20-29.9				<20	
White Blood Count (in 1000/mm ³)	≥40				20-39.9		15-19.9		3-14.9				1-2.9				<1	
Glasgow-Coma-Scale (GCS)	Score = 15 minus actual GCS																	
Serum HCO ₃ (venous, mmol/l, use if no ABGs)	≥52		41-51.9				32-40.9		22-31.9				18-21.9		15-17.9		<15	
A = Total Acute Physiology Score APS	Sum of the 12 individual variable points																	
B = Age Points	C = Chronic Health Points																	
≤44 years 0 points 45-54 years 2 points 55-64 years 3 points 65-74 years 5 points ≥75 years 6 points	If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows: a. For nonoperative or emergency postoperative patients – 5 points b. For elective postoperative patients – 2 points																	
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)																		

(From: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29)

APPENDIX B: RICHMOND AGITATION SCORE (RASS)²

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)	Verbal stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical stimulation
-5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment

1. Observe patient
 - Patient is alert, restless, or agitated. Score 0 to +4
2. If not alert, state patient's name and say to open eyes and look at speaker.
 - Patient awakens with sustained eye opening and eye contact. Score -1
 - Patient awakens with eye opening and eye contact, but not sustained. Score -2
 - Patient has any movement in response to voice but no eye contact. Score -3
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
 - Patient has any movement to physical stimulation. Score -4
 - Patient has no response to any stimulation. Score -5

APPENDIX C: Sample Standard Operating Procedure: Intermittent Bolus Feeding

A) **Location:** YSC or SRC MICU

B) **Eligibility:** Patients over 18 years of age admitted to the MICU at YSC or SRC mechanically ventilated with preserved GI function who have an enteral feeding initiation order placed by the primary team. See Table 3 and 4 for full inclusion and exclusion criteria.

C) Enrollment Process

- a) Research group to screen patients admitted to the MICU daily for inclusion/exclusion
- b) Waiver of consent obtained from IRB
- c) If eligible, treating team will be notified first (but can decide AGAINST intermittent feeding if special concerns as above)
- d) If an eligible patient is admitted, and decision to initiate enteral feeding is made by the primary team, the ICU nutritionist will confirm with research group re: inclusion/exclusion and if included, will provide recommendations for MEAL and SNACK volume versus 24 hour continuous feeding (current institutional default)
- e) There will be NO NEW enrollees on Saturday or Sunday (if already enrolled in study and receiving intermittent feeding this will continue over weekend as well)

D) Nursing Guidelines

- (1) Pour 24 hour total feeding volume as specified by Registered Dietician (RD) into enteral feeding bag
- (2) Start with the next closest meal or snack time
 - Meal times: 6AM, NOON, 6PM
 - Snack times: 9AM, 3PM, 9PM
- (3) The RD note will specify what each meal or snack volume should be. Meals are 65-75% of 24 hour volume, divided over 3 sessions. Snacks are 25-35% of 24 hour volume, divided over 3 sessions. **The FIRST SNACK or MEAL given should be 50% of target volume.**

Example Case: RD prescription notes Pivot 1.3 cal/cc formula. Meal goal: 350cc each, Snack goal: 150cc each. It is now 2PM.

Step 1: Pour 1500cc (350 x3 PLUS 150 x3; 24 hour total volume) into bag

Step 2: Plan on giving **first snack** at 3PM

Step 3: Give as intermittent bolus feed using max rate of 400cc/hr (which is 6.5 cc/min, equivalent to a little over a teaspoon every minute). First snack should be 50% of target volume (which is 150cc for snacks). This means the patient will receive 75cc of feeds as a snack in approximately 11 minutes.

Step 4: At 6PM the patient will be due for their **first meal**. First meal should be 50% of target volume also (which in this case was 350cc). This means the patient will receive 175cc of feeds as a meal using max bolus feeding rate of 400cc/hr (6.5cc/min). Volume should infuse in about 25 minutes.

- (4) If the first snack **AND** first meal given at 50% volume went well, for the next snack and meal titration up will continue. The volume will go up to 75% of target.

Example Case:

Step 5: If the preceding 3PM and 6PM feedings went well, for the next snack/meal you may titrate up to 75% of the goal volume. This would be for the 9PM snack, and next meal 6AM breakfast meal. Bolus feeding rate will be the same as prior.

- (5) If the second snack **AND** first meal given at 75% volume went well, for the next snack and meal titration up will continue. The volume will go up to 100% of target.

Example Case:

Step 5: If the preceding 9PM and 6AM feedings went well, for the next snack/meal you may titrate up to 100% of the goal volume. This would be for the 9AM snack, and next meal 12PM lunch meal. Bolus feeding rate will be the same as prior.

Titration Table

	Volume	Rate
First Snack or Meal	50% target	400cc/hr
First Snack or Meal (if started with snack, this would be meal or vice versa)	50% target	400cc/hr
Second Snack or Meal	75% target	400cc/hr
Second Snack or Meal (if started with snack, this would be meal or vice versa)	75% target	400cc/hr
Third Snack or Meal	100% target	400cc/hr
Third Snack or Meal (if started with snack, this would be meal or vice versa)	100% target	400cc/hr

What do I do if I encounter intolerance? What is enteral feeding intolerance?

Intolerance includes: abdominal pain, distension, vomiting, aspiration. Diarrhea can also be a sign of intolerance (although in the critically ill there may be other factors to consider as reasons for diarrhea). It is rarely severe enough to stop feeding. Please document instances of perceived enteral feeding intolerance.

Gastric residual volumes (GRV) are no longer recommended to be routinely checked (SCCM/ASPEN updated nutrition guidelines for adult ICU patients from 2016). If still checking GRV due to institutional culture, only >500cc PAIRED with symptoms is considered significant (**which is our current standard**)

(6) If there is concern for intolerance during a meal or snack at any point, may go back to the last tolerated volume and rate and slow down the titration (assure 2 successful sessions at those parameters before moving on)

Similarly, if there is concern for refeeding syndrome titration could be similarly slowed down

Example Case:

Step 6: If the patient did not tolerate the 100% **meal** volume, you would go back to the last tolerated volume in which the patient reliably tolerated both a meal and snack (in this case 75% of target) and ensure 2 successful sessions (i.e. 2 snacks and 2 meals) at this volume before moving on. **If there is still signs of intolerance** there can be consideration for adjuncts such as Reglan and/or erythromycin, and potentially modifiable risk factors that may be contributing to ileus (such as high dose narcotic infusion) should be discussed. **The RN may call the resource number listed for the research team.**

Titration Table (Intolerance)

	Volume	Rate	Observation	Action
First Snack	50% target	400cc/hr	tolerates	
First Meal	50% target	400cc/hr	tolerates	
Second Snack	75% target	400cc/hr	tolerates	

Second Meal	75% target	400cc/hr	tolerates	
Third Snack	100% target	400cc/hr	tolerates	
Third Meal	100% target	400cc/hr	INTOLERANCE encountered	
DE-ESCALATE/SLOW DOWN				
Fourth Snack	75% target	400cc/hr	tolerates	Go back to last tolerated % volume for BOTH snack and meal
Fourth Meal	75% target	400cc/hr	tolerates	
Fifth Snack	75% target	400cc/hr	tolerates	Make sure tolerates at this volume for 2 snacks and 2 meals
Fifth Meal	75% target	400cc/hr	tolerates	
Sixth Snack	100% target	400cc/hr	tolerates	Continue up-titration. Rechallenge 100%
Sixth Meal	100% target	400cc/hr	INTOLERANCE encountered again	Call resource number
Seventh Snack	100% target	400cc/hr	tolerates	Try again at 100% target but with adjunct (e.g. reglan) before reducing volume again
Seventh Meal	100% target	400cc/hr	tolerates	
Eighth Snack	100% target	400cc/hr	tolerates	Stay at 100%
Eighth Meal	100% target	400cc/hr	tolerates	

What do I do with my free water flushes that are separately ordered by the team?

In general, the 24 hour flush infusion practice is being phased out. Per updated nursing guidelines, each medication is now being flushed separately, if given enterally with 30cc of flush volume. (i.e. 8 tablets = 240cc of flushes). This medication flush volume should be charted so that the team can account for flush volumes already being given.

If the patient recently received a large flush volume (>250cc) for meds or for management of hypernatremia, there should be a **60 minute interval** between that flush

volume and the next snack/meal. To accomplish this, the snack/meal time can be ‘moved’ by +/- 30 minutes, and an effort should be made to slightly push back or push forward the flush timings to create a 1 hour interval.

Example Case:

Step 7: If the patient received 300cc as free water flushes at 8:30AM, the next meal which would have been a ‘snack’ at 9AM can be shifted back to 9:30AM. Alternatively, if the flushes were anticipated to occur at 9AM, an effort should be made to deliver the flush volume at 8:30AM instead whenever possible, so that the ‘snack’ could be given around 9:30AM (to allow for the approximate one hour interval).

What do I do if my patient is away for a test (or in a procedure) and missed a meal/snack?

If there is an opportunity to catch up within 30 minutes of the SCHEDULED snack/meal time, this should be done. Otherwise, if it’s been more than 30 minutes, that snack/meal should be simply skipped, and the patient would be fed the next bolus scheduled bolus nutrition.

Example Case:

Step 8: The patient is due for a ‘lunch’ meal at noon, but is off the floor for an MRI. The patient returns at 2PM. The ‘lunch’ noon meal should simply be skipped at that point, and the patient should receive the next scheduled bolus nutrition at 3PM as a ‘snack’.

If the patient returned to the floor at 12:30PM, a catch up ‘lunch’ could be given at that point. As with the adjustment for flushes above, meals/snacks can be moved up or down by 30 minutes from the scheduled time to accommodate work flow, testing etc. After the 12:30PM late lunch, feeding would proceed as planned (e.g. next would be 3PM snack).

What do I do if my patient has uncontrolled hyperglycemia and needs to go on insulin drip?

Example Case:

Step 9: The patient had been reasonably well controlled on high dose sliding scale insulin but now with increasing insulin resistance due to illness and also started on steroids. The team makes a decision to start an insulin infusion protocol (not DKA/HHNK). The Yale insulin infusion protocol (IIP) notes “begin in any ICU patient with more than 2 BGs >180mg/dl who is not expected to rapidly normalize their glycemic status. **Patients who are eating**, transferring out of ICU imminently, or pre-terminal or being considered for CMO status are **not generally a candidate for this IIP**”. In this instance we would consider the ‘bolus’ enteral feeding similar to a patient who is eating. While the insulin protocol allows for some exception to this rule to allow select patients who are ‘eating’ to still be on insulin infusion protocol (item 9 in guideline reads: ‘in the rare patient who is eating, consider giving SQ aspart PC to ‘cover’ the meal. In this circumstance don’t increase infusion rate during the first 3 hours PC.’), for the purposes of this pilot feeding study, those who are increasingly hyperglycemic who need insulin infusion will then be transitioned over to continuous enteral feeding to avoid unpredictable fluctuations in BGs and complex insulin infusion titration.

What do I do if have to hold feeds for certain medications? (Synthroid, Dilantin)

Example Case:

Step 10: Patients who require feeding holds due to a select set of medications like Synthroid or Dilantin will have the medication administration time manually

adjusted by the ICU pharmacist so that the snack/meal times can remain the same. For example the default medication administration time for Synthroid is currently at 6AM. This would coincide with the breakfast meal. The Synthroid dose might be moved to 8AM to ensure that the patient is not fed for the 1 hour before and 1 hour after medication administration.

My patient is now extubated. S/he is not yet ready to eat on their own and feeding will continue. What do I do?

Example Case:

Step 11: If the patient is extubated, but is deemed NOT yet ready to eat on their own, provided they still have an enteral feeding tube (in the stomach, NOT jejunum) they can continue on their intermittent bolus feeding protocol.

Who do I call with questions during nights or weekends?

In general, NEW patient recruitment will NOT occur over the weekend. Patients who were already enrolled during the weekday and started on intermittent bolus feeding will CONTINUE to be fed in that manner. If a question occurs over the weekend, members listed in the resource contact list can be tried.

For nights, a select group of night intensivist attendings have been in-serviced with regard to the pilot project in detail and can also be approached with questions for the nights they are on duty (listed in resource contact list pool). If a night time issue occurs on a night when one of these core night intensivists are NOT on duty (and a solution cannot be found after reviewing common questions/FAQs on the SOP), then the question should be reserved until the morning when the rest of the resource pool team can be contacted.

My patient is long term trach'd but not usually on the ventilator and had been eating at home. Is s/he eligible?

Yes. If the patient was previously eating by mouth, then they are eligible for this study. If the patient has a chronic feeding tube and receives most (or all) of their nutrition via the tube, they will NOT be eligible for this study. This includes patients who eat minimally by mouth for pleasure, and receives the bulk of the nutrition via a enteral feeding tube.

APPENDIX D: Yale-New Haven Health System Critical Care Insulin Infusion Protocol For Adults³

YNHHS Critical Care Insulin Infusion Protocol, Reviewed by Formulary Integration Committee (FIC) March 2016, June 2017

Yale-New Haven Health System



Critical Care Insulin Infusion Protocol (IIP) for Adults

*The following IIP is intended for use in hyperglycemic adult patients in the ICU or being transferred to the ICU from the PACU or ED. It should **NOT** be used in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), as these patients may require higher initial insulin doses, IV dextrose at some point, and important adjunctive therapies for their fluid/electrolyte/acid-base status. In any patient with BG >500 mg/dL, the initial orders should also be carefully reviewed with the MD, since a higher initial insulin dose and additional monitoring/therapy may be required. If the patient's response to the insulin infusion is at any time unusual or unexpected, or if any situation arises that is not adequately addressed by this protocol, the MD must be contacted for assessment and further orders.*

Getting Started

- 1.) PATIENT SELECTION: Begin IIP in any critically ill patient with more than 2 BGs ≥ 180 mg/dL who is not expected to rapidly normalize their glycemic status. Patients who are eating (see #9 below), transferring out of ICU imminently (<24 hrs), or pre-terminal or being considered for CMO status are not appropriate candidates for this IIP. In the CCICU only, IIP initiation threshold is a single BG ≥ 160 mg/dL.
- 2.) TARGET BLOOD GLUCOSE (BG) RANGE: **120-160 mg/dL**
- 3.) ORDERS: MD order required for use in the ICU.
- 4.) INSULIN INFUSION SOLUTION: Obtain from pharmacy (1 unit Regular Human Insulin / 1 cc 0.9 % NaCl).
- 5.) PRIMING: Before connecting, flush 20 cc infusion through all tubing.
- 6.) ADMINISTRATION: Via infusion pump in 0.5 units/hr increments.
- 7.) BOLUS & INITIAL INFUSION RATE: Divide initial BG level by 100, then round to nearest 0.5 units for bolus AND initial infusion rate.
Examples: 1.) Initial BG = 325 mg/dL: $325 \div 100 = 3.25$, round \uparrow to 3.5: IV bolus 3.5 units + start infusion @ 3.5 units/hr.
2.) Initial BG = 274 mg/dL: $274 \div 100 = 2.74$, round \downarrow to 2.5: IV bolus 2.5 units + start infusion @ 2.5 units/hr.
- 8.) CAUTION: If enteral/parenteral (TPN, PPN, Tube feeds) nutrition abruptly stopped, reduce infusion rate by 50%.
- 9.) Patients requiring IV insulin are usually not eating. If eating, consider giving SQ Aspart PC to "cover" the meal (1 unit/15 grams carbohydrates consumed (usual dose 3-6 units). Dose may be adjusted proportionate to the percentage of the tray consumed (e.g., $\frac{1}{2}$ dose if $\frac{1}{2}$ tray eaten).
- 10.) Patients with T1DM, insulin-requiring T2DM, and those requiring >1 unit/hr should be transitioned to scheduled SQ insulin (i.e. **NOT** just regular insulin sliding scale) prior to discharge from ICU. Please contact Pharmacy or refer to the Pharmacy Intranet for the Transition Guidelines.

BG Monitoring

While on infusion, use glucose meter to check BG hourly. Once stable (3 consecutive values in target range), may reduce checks to q 2 hr. If stable for 12-24 hrs, may space checks to q 4 hr. Resume hourly checks until stable again if: any BG out of range; any change in insulin infusion rate; any significant change in clinical condition; initiation/discontinuation of steroids, pressors, TPN/PPN/tube feeds, dialysis, CVVH, or CAVH. In patients who are vasoconstricted/hypotensive, capillary BG (i.e., fingersticks) may be inaccurate; venous or arterial blood is preferred in this setting.

Adjusting Infusion Rate

If BG < 50 mg/dL:

HOLD INSULIN INFUSION & administer 1 amp (25 g) D50 IV; recheck BG q 15 minutes until ≥ 90 mg/dL.

- Then, recheck BG q 1 hr; when ≥ 140 mg/dL, wait 30 min, then restart infusion at 50% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG 60-74 mg/dL:

HOLD INSULIN INFUSION & administer 1/2 Amp (12.5 g) D50 IV; recheck BG q 15 minutes until ≥ 90 mg/dL.

- Then, recheck BG q 1 hr; when ≥ 140 mg/dL, wait 30 min, then restart infusion at 50% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG 75-99 mg/dL:

HOLD INSULIN INFUSION. Recheck BG q 15 minutes until BG reaches or remains ≥ 90 mg/dL.

- Then, recheck BG q 1 hr; when ≥ 140 mg/dL, wait 30 min, then restart infusion at 75% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG \geq 100 mg/dL:

STEP 1: Determine the CURRENT BG LEVEL - identifies a COLUMN in the table:

BG 100-119 mg/dL	BG 120-159 mg/dL	BG 160-199 mg/dL	BG \geq 200 mg/dL
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STEP 2: Determine the RATE OF CHANGE from the prior BG level - identifies a CELL in the table - Then move right for **INSTRUCTIONS**:
[Note: If the last BG was measured 2 or more hrs before the current BG, calculate the hourly rate of change. Example: If the BG at 2PM was 150 mg/dL and the BG at 4PM is 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is $-30 \text{ mg/dL} \div 2 \text{ hours} = -15 \text{ mg/dL/hr}$.]

BG 100-119 mg/dL	BG 120-159 mg/dL	BG 160-199 mg/dL	BG \geq 200 mg/dL	INSTRUCTIONS*
		BG \uparrow by $> 60 \text{ mg/dL/hr}$	BG \uparrow	\uparrow INFUSION by "2 Δ "
	BG \uparrow by $> 40 \text{ mg/dL/hr}$	BG \uparrow by 1-60 mg/dL/hr OR BG UNCHANGED	BG UNCHANGED OR BG \downarrow by 1-20 mg/dL/hr	\uparrow INFUSION by " Δ "
BG \uparrow	BG \uparrow by 1-40 mg/dL/hr, BG UNCHANGED, OR BG \downarrow by 1-20 mg/dL/hr	BG \downarrow by 1-40 mg/dL/hr	BG \downarrow by 21-60 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED OR BG \downarrow by 1-20 mg/dL/hr	BG \downarrow by 21-40 mg/dL/hr	BG \downarrow by 41-60 mg/dL/hr	BG \downarrow by 61-80 mg/dL/hr	\downarrow INFUSION by " Δ "
BG \downarrow by $> 20 \text{ mg/dL/hr}$ see below†	BG \downarrow by $> 40 \text{ mg/dL/hr}$	BG \downarrow by $> 60 \text{ mg/dL/hr}$	BG \downarrow by $> 80 \text{ mg/dL/hr}$	HOLD x 30 min, then \downarrow INFUSION by "2 Δ "

†HOLD INSULIN INFUSION;
 $\sqrt{\text{BG}}$ in 15 min to be sure
 $\geq 90 \text{ mg/dL}$. Then recheck BG
 q 1 hr; when $\geq 140 \text{ mg/dL}$,
 restart infusion @75% of most
 recent rate, rounded down to
 the nearest 0.5 unit/hr.

STEP 3: CHANGES IN INFUSION RATE* (" Δ ")
 are determined by the current rate:

Current Rate (Units/hr)	Δ = Rate Change (Units/hr)	2 Δ = 2X Rate Change (Units/hr)
< 3.0	0.5	1
3.0 – 6.0	1	2
6.5 – 9.5	1.5	3
10.0 – 14.5	2	4
15 – 19.5	3*	6*
$\geq 20^*$	4*	8*

ALERT!!!

Except for hypoglycemia, NEVER
 terminate infusion unless transition orders
 to SQ insulin are in place! Any patient with type 1
 diabetes, on insulin before admission, or requiring
 $> 1.0 \text{ units/hr}$ should be transitioned to
 basal-bolus-correction (BBC) SQ insulin.
 Overlap with infusion by 2-3 hrs.
 (See 'YNHH Transition Guideline from
 IV Insulin Infusion')

* Depending on the clinical circumstances, infusion rates typically range between 2-12 units/hr.
 Doses $> 20 \text{ units/hr}$ are unusual, and, if required, the responsible MD should be notified to explore
 other potential contributing factors (including technical problems, such as dilution errors, etc.)

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APPENDIX E: Sample Size Calculator⁴

Sample Size, n_B <input type="text" value="71"/>	Power, $1 - \beta$ <input type="text" value="0.80"/>	Type I error rate, α <input type="text" value="5%"/>
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<input type="text" value="2.4"/>	Group 'A' mean, μ_A
<input type="text" value="3.2"/>	Group 'B' mean, μ_B
<input type="text" value="1.7"/>	Standard Deviation, σ
<input type="text" value="1"/>	Sampling Ratio, $\kappa = n_A/n_B$

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